IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of
CHANG et al

Serial No: 10/126,790

Filed: April 19, 2002

For: COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE

Group Art Unit: 1614

Examiner: Brian S. Kwon

Confirmation No. 3467

DECLARATION OF PRIOR INVENTION IN THE UNITED STATES OR IN A NAFTA OR WTO MEMBER COMPANY TO OVERCOME CITED PATENT OR PUBLICATION (37 C.F.R. § 1.131)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PURPOSE OF DECLARATION

1. This declaration is to establish completion of the invention in this application in the United States, at a date prior to July 14, 2000, that which is earlier than the effective dates of the prior art publications that were cited by the examiner.

2. The persons making this declaration are the inventors.

FACTS AND DOCUMENTARY EVIDENCE

To establish the date of completion of the invention of this application, the enclosed copies of parts of an Allergan, Inc., R&D documents (8 pages), signed by several individuals are submitted as evidence. The first two pages establish that a formulation called 9262X was known by these individuals. The third page shows that the formulation 9262X is identical to the formulation used in the clinical study described in the patent. The last five pages show that formulation 9262X was known to have utility in treating patients.

From these documents, it can be seen that the invention in this application was made at least by the date of July 14, 2000, which is a date earlier than the effective date of the references.

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express Mail (Label No. EL979880572US) in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 27, 2004.

Printed name of person making deposit: Adriane Giberson

Signature: Adriane Giberson Date: July 27, 2004

TIME OF PRESENTATION OF THE DECLARATION

This declaration is submitted prior to final rejection.

DECLARATION

6. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

7. Inventor(s)

Full name of sole or first inventor: Chin-Ming Chang

Inventor's signature: _____ Date: 7/20/04
Country of Citizenship: Taiwan
Residence: Tustin, California
Post Office Address: 11645 Maynard Avenue, Tustin, California 92782

Full name of second joint inventor: Gary J. Beck

Inventor's signature: _____ Date: 26 July 04
Country of Citizenship: USA
Residence: Fullerton, California
Post Office Address: 2085 Smokewood Ave., Fullerton, CA 92831

Full name of third joint inventor: Cynthia C. Pratt

Inventor's signature: _____ Date:
Country of Citizenship: USA
Residence: Mission Viejo, California
Post Office Address: 23436 Ancia Lane, Mission Viejo, California 92691

Full name of fourth joint inventor: Amy L. Batoosingh

Inventor's signature: _____ Date: 20 Jul 04
Country of Citizenship: USA
Residence: Mission Viejo, California
Post Office Address: 28472 Casanal, Mission Viejo, California 92692

ALLERGAN, INC.
RESEARCH & DEVELOPMENT
PHARMACEUTICAL SCIENCES
PHARMACEUTICAL DEVELOPMENT

MEMORANDUM

TO	D. Marsh, B. Lima, L. Grau, B. Housholder, M. Bojorquez
CC	A. Syracuse, C. Anger, J. Fleitman, L. Gryziewicz, J. Chang
FROM	C.M. Chang
SUBJECT	Revisions to the Stability Protocol PD-1999-19: Protocol to Monitor Registration Stability Batches of Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Ophthalmic Solution (9262X)
DATE	

The stability protocol PD-1999-19 has been revised to reflect the following minor changes:

- Renamed the sub-lot titles: C1 and C2 to B3 and B4; D1 and D2 to C1 and C2; E1 and E2 to D1 and D2; and F to E.
- Corrected the tip part number from 40979 to 40979-9.
- Updated number of units required for the release assays.

Chin-Ming Chang

X 5902

ALLERGAN PHARMACEUTICALS

PHARMACEUTICAL R&D

PHARMACEUTICAL SCIENCES

LIQUID FORMULATIONS

PROTOCOL NUMBER

PD-1999-19

PROTOCOL TO MONITOR REGISTRATION STABILITY BATCHES OF BRIMONIDINE TARTRATE 0.2%/TIMOLOL 0.5% COMBINATION OPHTHALMIC SOLUTION (9262X)

Issued:

Author: _____ Date
C.M. Chang, Sr. Scientist, Liquid Formulations

Author: _____ Date
D. Marsh, Department Manager, Stability, Pharmaceutical Analysis

Reviewed By: _____ Date
B. Lima, Sr. Scientist, Pharmaceutical Analysis

Approved by: B. Lima for A. Syracuse
A. Syracuse, Director, PSQA Date

Approved by: _____ Date
C. Anger, Director, Research Microbiology

Approved By: _____ Date
J. Fleitman, Director, Pharmaceutical Analysis

Approved By: _____ Date
L. Gryziewicz, Director, Regulatory Affairs

Approved By: _____ Date
J. Chang, Manager, Liquid Formulations

REQUIREMENTS

COMPOSITION

BRIMONIDINE TARTRATE 0.2%/TIMOLOL 0.5% COMBINATION OPHTHALMIC SOLUTION (9262X)

Ingredients	Grade	% w/v
Brimonidine Tartrate	N/A	0.2[a]
Timolol Maleate	USP/ Ph.Eur.	0.68[b]
Benzalkonium Chloride	NF/Ph.Eur.	0.005
Sodium Phosphate Monobasic Monohydrate	USP	0.43
Sodium Phosphate Dibasic Heptahydrate	USP	2.15
Hydrochloric Acid[c]	NF/Ph.Eur.	pH 6.9
Sodium Hydroxide[c]	NF/Ph.Eur.	pH 6.9
Purified Water	USP/Ph.Eur.	QS

[a] Equivalent to 0.132% w/v of brimonidine free base.
[b] Equivalent to 0.5% w/v of timolol free base.
[c] Pharmacopeial grade hydrochloride acid and sodium hydroxide are prepared into 1 N solutions for pH adjustments.

PRODUCT PRIMARY CONTAINER CLOSURE SYSTEMS

Component	Part Number	Supplier	Description	Mode of Sterilization
Bottle	21472-9	Medical Plastics	Bottle, Boston Round, 8 mL, white LDPE, Sophia, Particulate reduced.	EtO
Bottle	21613-9	Medical Plastics	Bottle, Boston Round, 15 mL, white LDPE, Sophia, Particulate reduced.	EtO
Tip	40979-9	Medical Plastics	Tip dropper, 15 mm, 28 µL, white LDPE, particulate reduced.	EtO
Cap	30402-9	Medical Plastics	Cap, Polystyrene, 15 mm, Blue	EtO
Ampule[a]	—	PSO	Clear, 5cc class A borosilicate glass	Steam and/or Dry Heat
Label	52164LH10E (8 mL)	H.S. Crocker	Fasson E828 adhesive PMS 247 and 281 ink colors No varnish.	N/A
Label	52165LH10E (15 mL)	H.S. Crocker	Fasson E828 adhesive PMS 247 and 281 ink colors No varnish.	N/A

[a] Drug product is filled in ampules as a control for extractables testing.

CLINICAL STUDY REPORT

A MULTICENTER, INVESTIGATOR-MASKED, RANDOMIZED, PARALLEL STUDY OF THE SAFETY, TOLERABILITY AND EFFICACY OF TWICE-DAILY DOSED 0.2% BRIMONIDINE TARTRATE/0.5% TIMOLOL COMBINATION COMPARED WITH TWICE-DAILY DOSED TIMOPTIC® OR THREE-TIMES-DAILY DOSED ALPHAGAN® FOR SEVEN DAYS IN SUBJECTS WITH GLAUCOMA OR OCULAR HYPERTENSION

Study Number: 190342-011T

Allergan Signatory: Scott M Whitcup _____

Scott M Whitcup, MD, Vice President
Ophthalmology Therapeutic Area

Date

1.0 TITLE PAGE

CLINICAL STUDY REPORT

A Multicenter, Investigator-Masked, Randomized, Parallel Study of the Safety, Tolerability and Efficacy of Twice-Daily Dosed 0.2% Brimonidine Tartrate/0.5% Timolol Combination Compared with Twice-Daily Dosed Timoptic® or Three-Times-Daily Dosed ALPHAGAN® for Seven Days in Subjects with Glaucoma or Ocular Hypertension

Study Number: 190342-011T-00, **Phase:** 2

Study Initiation Date:

Study Completion Date:

Allergan Responsible Medical Officer:	Joseph Lambert, MD, Ophthalmology Clinical Research
Allergan Signatory:	Scott Whitcup, MD, Vice President Ophthalmic Drug Development

Sponsor: Allergan, Inc, 2525 Dupont Drive, Irvine, California 92623-9534, USA; Telephone (714) 246-4500

This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki.

2.0 SYNOPSIS

Name of Company: Allergan	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brimonidine tartrate 0.2%/Timolol 0.5%	Page:	

Number and Title of Study:
190342-011T: A Multicenter, Investigator-Masked, Randomized, Parallel Study of the Safety, Tolerability, and Efficacy of Twice-Daily Dosed 0.2% Brimonidine tartrate/0.5% Timolol Combination Compared with Twice-Daily Dosed Timoptic® or Three-Times-Daily Dosed ALPHAGAN® for Seven Days in Subjects with Glaucoma or Ocular Hypertension

Investigators: Douglas Day, MD; Kenneth Sall, MD; William Stewart, MD

Study Center(s): 3 US Sites

Publication (reference): None

Studied Period (years): (date of first enrollment) (date of last completed)	Phase of Development: 2

Objectives:
To evaluate the safety, tolerability and efficacy of twice-daily dosed brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution combination (henceforth referred to as Combination) compared with that of twice-daily dosed Timoptic® (henceforth referred to as Timolol) or three—times-daily dosed ALPHAGAN® (henceforth referred to as Brimonidine) administered for 7 days in patients with glaucoma or ocular hypertension.

Methodology:
Structure: multicenter, investigator-masked, randomized, parallel-group, active control
Randomization: at each site, patients were randomized to one of the 3 masked treatment groups (Combination, Brimonidine or Timolol) based on an even allocation
Visit Schedule: prestudy, day 0 (baseline), day 1 (dosing), day 4 and day 7

Number of Patients (Planned and Analyzed):
66 planned; 73 enrolled (Combination = 25, Brimonidine = 25, Timolol = 23); 72 completed.

Mean (range) age: 59.9 (30.7 to 82.1) years; 39.7% (29/73) males, 60.3% (44/73) females.

Diagnosis and Main Criteria for Inclusion:
Diagnosis: ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma and requiring bilateral administration of treatment.

Key Inclusion Criteria: ≥ 21 years, day 0 (post-washout) intraocular pressure (IOP) ≥ 22 mm Hg and ≤ 34 mm Hg in each eye and asymmetry of IOP ≤ 5 mm Hg, best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score equivalent to a Snellen score of 20/100 or better in each eye.

Key Exclusion Criteria: uncontrolled systemic disease, abnormally low or high blood pressure or pulse rate for age or contraindication to beta-adrenoceptor antagonist therapy, anticipated alteration of existing chronic therapy with agents which could have a substantial effect on IOP, contraindication to brimonidine therapy, allergy or sensitivity to any of the study medication ingredients, anticipated wearing of contact lenses during the study, laser surgery, intraocular filtering surgery or any other ocular surgery within the past 3 months, or required chronic use of other ocular medications during the study (intermittent use of artificial tear product was allowed).

Test Product, Dose and Mode of Administration, Batch Number:
Brimonidine tartrate 0.2%/Timolol 0.5% ophthalmic solution (9216X), one drop (28 µL) instilled in each eye twice-daily (BID)

SYNOPSIS (page 2 of 3)

Name of Company: Allergan	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brimonidine tartrate 0.2%/Timolol 0.5%	Page:	

Duration of Treatment: 7 days

Reference Therapy, Dose and Mode of Administration, Batch Number:
Active control ALPHAGAN® (brimonidine tartrate) 0.2% (7831X); one drop (28 µL) instilled in each eye three-times-daily (TID)

Active control Timoptic® (timolol) 0.5% (6151X); one drop (28 µL) instilled in each eye BID

Criteria for Evaluation:
Efficacy:
Diurnal IOP (hours 0, 2, 4, 7, 9 and 12), clinical success questionnaire, patient comfort and satisfaction questionnaire.

Safety:
Adverse events (AE), heart rate, blood pressure, visual acuity (VA), biomicroscopy.

Statistical Methods:
The safety population comprised all randomized and treated patients, and was used for baseline characteristics and safety analyses. The modified intent-to-treat (ITT) population used for efficacy analyses comprised all randomized and treated patients with at least one post-baseline assessment of efficacy.

Missing values were not imputed unless stated otherwise. All by-visit analyses were based on observed values at each visit. In addition to the analysis of observed cases in the modified ITT population defined in the protocol, the primary efficacy endpoint IOP was also analyzed applying Last Observation Carried Forward (LOCF) to all randomized patients. Results were summarized with tabulations and case listings. Categorical variables (such as VA and biomicroscopic severity) were summarized with descriptive statistics. Continuous variables (such as IOP change from baseline) were analyzed using one way analysis of variance (ANOVA), or nonparametric methods as appropriate. For each question in the Patient Comfort/Satisfaction and Clinical Success Questionnaires, the number and percent of patients for each possible response was listed.

All hypothesis tests were 2-sided, with p-values less than or equal to 0.05 considered statistically significant for main effects.

Summary – Conclusions:
Efficacy:
Mean diurnal IOP at baseline was similar among the 3 treatment groups and ranged from 20.6 to 25.4 mm Hg for the Combination group, from 20.1 to 24.4 mm Hg for the Brimonidine group, and from 20.8 to 24.0 mm Hg for the Timolol group ($p \geq 0.230$). Within each treatment group, IOP at the different hours decreased significantly ($p \leq 0.05$) compared with baseline at each post-dose follow-up visit. Additionally, the Combination treatment decreased IOP by ≥ 3 mm Hg at each post-dose follow-up visit, which was considered to be clinically relevant.

At day 4, the mean decrease from baseline IOP and the mean IOP between hours 0 and 12 ranged from:
–4.7 to –7.6 mm Hg; 15.3 to 17.8 mm Hg for the Combination group
–3.4 to –5.9 mm Hg; 15.5 to 20.3 mm Hg for the Brimonidine group
–3.2 to –4.6 mm Hg; 17.6 to 19.4 mm Hg for the Timolol group

At day 7, the mean decrease from baseline IOP and the mean IOP between hours 0 and 12 ranged from
–4.9 to –7.8 mm Hg; 15.1 to 17.7 mm Hg for the Combination group,
–2.5 to –5.8 mm Hg; 15.1 to 20.7 mm Hg for the Brimonidine group
–2.9 to –5.1 mm Hg; 17.3 to 18.9 mm Hg for the Timolol group

Name of Company: Allergan	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brimonidine tartrate 0.2%/Timolol 0.5%	Page:	

Summary – Conclusions (Continued):

Efficacy (Continued):

Mean decrease from baseline IOP was greater for the Combination group than for the Brimonidine and Timolol groups at all hours on days 4 and 7. These mean decreases from baseline IOP were statistically significantly greater for the Combination group than that for the Brimonidine group at hour 0 on day 4 and hours 0, 4, and 7 on day 7; and statistically significantly greater than that for the Timolol group at hours 0, 2, 4, 9 and 12 on day 4 and hours 0, 2, 4 and 12 on day 7. Mean IOP was lower for the Combination group than for the Brimonidine and Timolol groups at all hours on day 4 and at all but one hour (hour 9) on day 7, although not all differences were statistically significant.

Clinical success reported by the investigator on day 7 was much higher for the Combination group (96.0%, 24/25 patients) than for the Brimonidine group (76.0%, 19/25 patients, p = 0.098) or the Timolol group (69.6%, 16/23 patients, p = 0.020). Overall, there were no statistically significant treatment group differences in comfort/satisfaction evaluation of the study medication by patients.

Safety:

Through the 7 days of treatment, 24.0% (6/25) of patients in the Combination group, 24.0% (6/25) of patients in the Brimonidine group, and 30.4% (7/23) in the Timolol group experienced 1 or more AEs, regardless of causality, with no statistically significant differences among groups (p = 0.843). A total of 20.0% (5/25), 20.0% (5/25) and 26.1% (6/23) of patients in the Combination, Brimonidine and Timolol groups, respectively, experienced 1 or more treatment-related AE. Overall, there was no statistically significant difference in the percentage of patients experiencing 1 or more treatment-related AEs among the 3 treatment groups (p = 0.880). The most common treatment-related AEs were burning eye and conjunctival hyperemia each reported for 8.0% (2/25) of patients in the Combination group, eye pruritus reported for 8.0% (2/25) of patients in the Brimonidine group, and burning eye reported for 8.7% (2/23) of patients in the Timolol group. The majority of AEs were ocular and mild in severity. There were no discontinuations due to AEs and no serious AEs or deaths reported during the study.

Changes in VA at follow-up compared to baseline (day 0) were not statistically significantly different among treatment groups for any visits, with most patients in each treatment group showing "no change" in VA. There were no clinically relevant VA observations. There were no statistically significant among-group differences in Biomicroscopy findings. Overall, 12.0% (3/25) of patients in the Combination group, 4.0% (1/25) of patients in the Brimonidine group, and 8.7% (2/23) of patients in the Timolol group had at least 1 severity grade increase from baseline in Biomicroscopy findings at 1 or more visits. Although there were some statistically significant ($p < 0.05$) differences in heart rate and blood pressure among and within groups, none of these changes were considered clinically relevant. There were no consistent trends in changes in heart rate or blood pressure observed for any of the treatment groups.

Conclusion:

The Combination treatment (brimonidine tartrate 0.2%/timolol 0.5%) administered BID for 7 days, was well tolerated in patients with glaucoma or ocular hypertension. The safety profile of the Combination treatment was comparable to that of the individual components, Brimonidine (ALPHAGAN®) and Timolol (Timoptic®). Short-term dosing with the Combination provided statistically significant and clinically relevant reduction of IOP. The mean decreases in IOP with the Combination were greater than with either Brimonidine or Timolol at all timepoints, although not all differences were statistically significant.

Date of Report:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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CHANG et al.

Serial No: 10/126,790

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Group Art Unit: 1614

Examiner: Brian S. Kwon

Confirmation No. 3467

DECLARATION OF AN EXPERT REGARDING FACTS RELEVANT TO PATENTABILITY (37 C.F.R. § 1.132)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PURPOSE OF DECLARATION

1. This declaration is to establish evidence of patentability of one or more claims of the above referenced application.

2. The persons making this declaration is an expert in the relevant art.

TESTIMONY OF EXPERT RELEVANT TO PATENTABILITY

3. The table attached herewith, labeled Table A, presents results which were obtained from a one-month clinical trial. In this clinical trial, patients were topically administered either 1) a composition containing 0.2% brimonidine and 0.5% timolol twice a day (Combination), 2) a 0.5% timolol composition twice a day and a 0.2% brimonidine composition three times a day (Concurrent), or 3) a 0.2% brimonidine composition three times a day (Alphagan). The percentage of patients in the Combination group experiencing adverse events of the nervous system (0.0%) is lower than the percentage of patients experiencing adverse events of the nervous system in both

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express Mail (Label No. EL979880572US) in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 27, 2004.
Printed name of person making deposit: Adriane Giberson
Signature: Adriane Giberson Date: July 27, 2004

TIME OF PRESENTATION OF THE DECLARATION

This declaration is submitted prior to final rejection.

DECLARATION

4. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

7. Expert in the Pharmaceutical Art

Full name expert: Rhett Schiffman, MD, MS, MHSA

Expert's signature: _____ Date: July 2, 2004
Country of Citizenship: USA
Residence: Laguna Beach , California
Post Office Address: 1743 Temple Hills Drive

TABLE A

All Adverse Events: Number (Percent) of Patients by Body System

(Safety Population)

Body System	Adverse Event (Preferred Term)	Combination (N=174)	Concurrent (N=167)	Alphagan (N=85)	P-value[a]
Digestive System	NAUSEA AND VOMITING	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Hemic and Lymphatic Syste	Overall	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
	ANEMIA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Metabolic and Nutritional Disorders	Overall	2 (1.1%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	PERIPHERAL EDEMA	1 (0.6%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	HYPERLIPEMIA	1 (0.6%)	0 (0.0%)	0 (0.0%)	>0.999 [b]
	HYPERGLYCEMIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
Musculoskeletal System	Overall	1 (0.6%)	1 (0.6%)	1 (1.2%)	0.804 [b]
	ARTHRALGIA	1 (0.6%)	0 (0.0%)	0 (0.0%)	>0.999 [b]
	MYALGIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	TRAUMATIC BONE FRACTURE	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Nervous System	Overall	0 (0.0%)	5 (3.0%)	5 (5.9%)	0.003 [b]
	SOMNOLENCE	0 (0.0%)	2 (1.2%)	2 (2.4%)	0.113 [b]
	DEPRESSION	0 (0.0%)	2 (1.2%)	0 (0.0%)	0.193 [b]
	DIZZINESS	0 (0.0%)	1 (0.6%)	2 (2.4%)	0.054 [b]
	ATAXIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	INSOMNIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	INCOORDINATION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Respiratory System	Overall	5 (2.9%)	6 (3.6%)	2 (2.4%)	0.850
	INFECTION SINUS	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.679 [b]
	SINUSITIS	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.679 [b]
	RHINITIS	1 (0.6%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	COUGH INCREASED	1 (0.6%)	0 (0.0%)	1 (1.2%)	0.513 [b]
	BRONCHITIS	0 (0.0%)	2 (1.2%)	0 (0.0%)	0.193 [b]

Note: All adverse events are represented, regardless of relationship to treatment.
Within each body system, preferred terms are sorted by descending frequencies of treatment groups from left to right.
Within each preferred term, a patient is counted at most once.

[a] A Pearson's chi-square test is performed to evaluate the equality of proportions among treatment groups unless otherwise noted.

[b] P-value is based on Fisher's exact test.